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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
			T37-612

EXAMINER

ART UNIT	PAPER NUMBER
	16

DATE MAILED: 09/25/01

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 6-25-01.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 32-61 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 32-61 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

★ U.S GPO: 1996-409-290/40029

DETAILED ACTION

1. The finality of the rejection of the last Office action is withdrawn in view of the new grounds of rejection set forth below.

Response to Amendment

2. The amendment filed 12 April 2001 (Paper No. 17) has been entered.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Applicant's arguments filed 25 June 2001 (Paper No. 19) in the appeal's brief have been fully considered but they are not found persuasive.

Priority

5. The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

The heading on the first line of page 1 refers to this application as a continuation but this application appears to have some subject matter which is different from the parent application. Thus, this application appears to be a continuation in part of the parent application.

6. Applicant's claim for domestic priority under 35 U.S.C. 120 is acknowledged. However, the parent application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 32-45 of this application.

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claims 32-53 and 56-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Written description rejection.

Claims 32-53 and 56-61 encompass a peptide comprising L1-L3 which are any hydrophobic amino acids. However However, the specification only discloses working example of species which have L1-L3 comprising leucine as the amino acid but do not disclose a working example of the genus of other amino acids which are hydrophobic. *University of California v. Eli Lilly and*

Co. (CAFC) 43 USPQ2d 1398 held that a generic claim to human or mammalian when only the rat protein sequence was disclosed did not have written description in the specification. Thus, the only disclosure to leucine in L1-L3 does not have written description for the genus of hydrophobic amino acid sequences. One skilled in the art at the time of the invention was only aware of the leucine motifs and not other hydrophobic amino acid motifs (Montminy, page 654). One skilled in the art at the time of the invention found that when alanine is substituted in place of leucine in the LXXLL motif in the P-2 peptide that it would not bind (Heery et al., page 735, figure 3). The essential feature of the invention is that L in the LXXLL motif must be the amino acid leucine.

8. Claims 32-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide sensor consisting of a peptide comprising LXXLL where the L is a leucine and has the sequence which interacts with a specific nuclear receptor, does does not reasonably provide enablement for a peptide sensor consisting of a peptide comprising LXXLL where the L is a hydrophobic amino acid or a peptide sensor consisting of a peptide comprising SEQ ID NO:11 and which interacts with any nuclear receptors including orphan nuclear receptor which does not have a ligand. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 54-55 are drawn to a peptide comprising SEQ ID NO:11 which does not work as disclosed in the specification on page 6 in Table 2. It would require undue experimentation to use a peptide consisting of SEQ ID NO:11 in the claimed method because Table 2 teaches that SEQ ID NO:11 does not work in the method.

Claims 18-20 and 23-37 encompass a peptide comprising L1-L3 as any hydrophobic amino acid. However, the specification does not teach using any hydrophobic amino acid for L1-L3. The specification teaches using L1-L3 with leucine in the working example but not with any hydrophobic amino acid substituted for leucine. It is known in the art that leucine amino acids play a special role in protein-protein interaction (Monminy, Nature 1997; Heery et al., Nature 1997). Heery et al. teach that P-2 peptide which has alanine substituted for leucine do not work (figure 3). Thus, it would require empirical and random experimentation to determine whether hydrophobic amino acids would have the same protein-protein interaction as in the co-activator and nuclear receptor interaction. It would require undue experimentation for one of skilled in the art to determine whether hydrophobic amino acids could be used to replace leucine.

Claims encompass using any nuclear receptors with the

peptide including orphan nuclear receptors. The claims 32-61 encompass a method using an orphan receptor with no known ligand. The specification on page 5, line 17-18, recite the usage with orphan receptor. Furthermore, many of the receptor listed in claim 46 and on pages 3-4 of the specification are orphan receptors such as GCNF, ERR, NURR1, ROR, and many others for which the ligands are not known and whose function is not known (Mangelsdorf et al., 1995). However, it would require undue experimentation to use an orphan receptor. It would require undue experimentation to use the peptide with an orphan receptor whose function and ligand is not known. Since the function of the protein is not known because the ligand is not known, the method of using the protein is not enabled. It would require empirical and random experimentation to determine the ligand and function for the receptor and then further test the receptor for its interaction with the orphan receptor. Different receptors would have different functions and the skilled artisan would have to determine the function of the orphan receptor. The claimed polypeptides are not enabled because the skilled artisan would need to prepare, isolate, and analyze the protein in order to determine its function and use. Therefore, the invention is not in readily available form. Instead, further experimentation of the protein itself would be required before it could be used. Furthermore, the interaction of peptide with receptor does not

work without the ligand (see Heery et al., figures 1 and 3).

Claim Rejections - 35 USC § 112, 2nd paragraph

9. Claims 32-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The terms "agent-biased binding" and "unbiased binding" in claim 32 is not defined in the specification. One skilled in the art generally describe pharmacological binding using terms such as "specific" or "non-specific" binding. For example, the sensor binds specifically to the receptor. However, it is not clear what the terms mean and the metes and bounds of the agent biased versus unbiased binding. Claims 33-61 are dependent on claim 32.

Claims 33-38 recites the limitation "the measuring step" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

10. Claims 32, 47, 49, 51, 53-55, and 58 are rejected under 35 U.S.C. 102(a) as being anticipated by Heery et al. (Nature, 1997)with evidence from Torchia et al.(Nature, 1997).

Heery et al. disclose two peptides comprising LXXLL motifs called P-1 which interact with SRC-1a and ER ligand binding domain fused to GST in the presence of E2 ligand(Figure 3; page 734, first column, bottom paragraph). Claim 32 sensor limitations are met by the peptides P-1 because the peptides are less than 24 amino acid residues in length and comprise the LXXLL motifs. The claim 32 process limitation is met since P-1 and P-2 interactions with co-activators SRC-1a and SRC-1a-M1234 and ER, estrogen receptor, which is a nuclear receptor. Claim 32 assay is taught by figure 3 because the term "not a natural coactivator protein of the receptor" is met by SRC-1a which is in vitro translated which is not natural. Claim 32 limitation "candidate agent" generically encompasses any compound which modulates or affects the binding function of the receptor such as the ligand or coactivators. Claim 32 limitation of "agent-biased binding" and "unbiased binding" controls with or without the ligand or the coactivator SRC1a. The mixture is met by the estrogen receptor, P1 or P2 peptide, and SRC1a protein which is the candidate agent. The mixture can also have the ligand which is met by E2 ligand. Claim 47 limitation of "agent effects an increase in binding" is

produced by either the E2 ligand or the coactivator. Claim 49 limitation of "in solution " is taught on page 736 of Heery et al. Claim 51 limitation of a ligand of the receptor is taught by the E2 or the coactivator because the term "ligand" generically encompass a molecule which interact with the receptor. Claims 54 and 55 limitation of SEQ ID NO:11 is disclosed and is the same sequence as the P-1 peptide (see figure 3b). The ligand used was E2 which binds the ER estrogen receptor. The P-1 peptides comprises additional amino acid residues covalently coupled to the LXXLL motif which can be directly detected in a UV spectrophotometer thus meeting the detectable label limitation of claim 58. Claim 53 limitation of comprising an amphipathic alpha helix is met because the P-1 and P-2 comprises the LXXLL motifs which inherently form the helical domain with amphipathic characteristics (see evidence of Torchia et al., page 680, second column, bottom paragraph).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 32, 47, 49, 51-55, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heery et al.(Nature, 1997) in view of Montminy (Nature, 1997), and Torchia et al. (Nature, 1997).

Heery et al. teaching and disclosure has been discussed above. Heery et al. teach the method of ligand activated nuclear receptor interaction with CBP/p300 coactivator and the discovery that LXXLL is the consensus interaction region sequence (Figures 1-3). Heery et al. describes that a short conserved motif contained within as few as eight amino acids is sufficient to bind to transcriptionally active nuclear receptors (page 733, second column, second paragraph, last line). Heery et al. do not disclose a peptide which is 12 or fewer residues in length of claim 19.

Montminy reviews Heery et al. and Torchia et al. references and teaches the importance of the finding in allowing for the eventual development of antagonists that can disrupt these complexes (page 655, second column).

Torchia et al. is a cumulative reference (see figure 6 and pages 683-684) with Heery et al. and Montminy. Torchia et al. teach that the demonstration that specific signal-transduction pathways has potentially intriguing applications to the study of signaling in development as well as therapeutic implications(page 683, second column, top paragraph, last line).

All of the parts of the claim limitations were well know to one of ordinary skill at the time of the invention. It would have been obvious to one of ordinary skill in the art at the time of the invention modify the peptides of Heery et al. to peptides smaller than 12 amino acid residues because one of ordinary skill in the art at the time of the invention would have been motivated by Heery et al teaching that a short conserved motif contained within as few as eight amino acids is sufficient to bind to transcriptionally active nuclear receptors (page 733, second column, second paragraph, last line). Heery et al. first discovered the novel concept that LXXLL motif is the important domain in the coactivators which allow receptor binding (figures 1a and 1b; figure 2a). Heery et al. further used P-1 peptide, a 14 amino acid residue containing the LXXLL motif, to show specific interaction to ER receptor (figure 3). Heery et al. teaching of eight amino acids if not a direct teaching and description of a smaller peptide containing the LXXLL motif then it is certainly motivation for making smaller peptides. Further

motivation is provided by Montminy and Torchia et al. who teach the importance of identifying ligands for therapeutic utility. Even more motivation is provided by Montminy (page 655, last line) teach that the identification of leucine rich motifs by Heery and Torchia allow for the eventual development of antagonists that can disrupt these complexes. The expectation of success is high because both Heery et al.(page 736) and Torchia et al.(page 863-864) make and use peptides from based on the LXXLL motif from coactivators to show binding to receptors.

13. Claims 32 and 47-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heery et al.(Nature, 1997) in view of Mathis (Clin. Chem., 1995), Montminy (Nature, 1997), Torchia et al. (Nature, 1997).

Heery et al. teaching and disclosure has been discussed above. Heery et al. teach the method of ligand activated nuclear receptor interaction with CBP/p300 coactivator and the discovery that LXXLL is the consensus interaction region sequence (Figures 1-3). Heery et al. do not teach a label which is an epitope tag of claim 24. Heery et al. do not teach the luminescent label which is a fluorescent label. Heery et al. does not teach a method where the label is measured using fluorescent polarization. Heery et al. do not teach a method of using a sensor at a concentration of 10 nM or less.

Montminy teachings have been discussed above.

Torchia et al. teachings have been discussed above. Torchia et al. teach the epitope tagging with His-tag and purification using nickel chelate chromatography (page 684, first column, second paragraph). Torchia et al. also teach generating antibodies by injecting purified proteins into rabbits(page 684, first column, second paragraph).

Mathis teaches the FRET with Jun-Fos dimerization including leucine zipper domain interaction as well as other protein dimerizations using Eu3+ and APC fluorescent reagents (page 1394-1395 and figure 6).

Pantoliano et al. teach a method of using fluorescent label to quantify ligand binding to receptor including nuclear receptor using fluorescent polarization (columns 8; column 14, line 50; column 15, lines 33-46; column 16, lines 25-67; column 17, lines 1-64; column 18, lines 14-24; column 20; columns 37-38).

Claims 56 and 57 limitations are drawn to a label which can be indirectly detected which specifically includes a label with a epitope tag.

One of ordinary skilled in the art would have been motivated to modify the peptides of Heery et al. to include an epitope tag because the ease in purification of the peptides by nickel chelate chromatography and ease of detection with antibodies.

Claims 59-61 limitations are drawn to a label which can be

directly detected which specifically includes a label which is a fluorescent label.

It would have been obvious to one of ordinary skill in the art at the time of the invention modify the peptides of Heery et al. by incorporating the teaching of Mathis of fluorescent labeling because one of ordinary skill in the art would have been motivated because of the teachings of Mathis that FRET allows real time correction for optical transmission and the assay is free from media interference (Page 1395, second column) which would allow an improved assay. One of ordinary skill in the art would also be motivated because Mathis teaching of Jun/Fos dimerization is an analogous art which teaches assay improvement using leucine rich motif dimerization studies with FRET especially since the protein interaction in both system is the leucine rich interactions. Further motivation is provided by Montminy and Torchia et al. who teach the importance of identifying ligands for therapeutic utility. Even more motivation is provided by Montminy (page 655, last line) teach that the identification of leucine rich motifs by Heery and Torchia allow for the eventual development of antagonists that can disrupt these complexes.

Claim 48 encompass a method using a sensor at a concentration of 10 nM or less.

It would have been obvious to one of ordinary skill in the

art at the time of the invention modify the method of Heery et al. by incorporating the teaching Mathis FRET which uses low concentration of labeled peptides(0.1 nM; figure 6) because one of ordinary skill in the art would have been motivated by the real time correction for optical transmission and where the assay is free from media interference (Page 1395, second column) which would allow for an improved assay.

Claim 50 encompass a method using a fluorescent polarization to detect the label.

It would have been obvious to one of ordinary skill in the art at the time of the invention modify the method of Heery et al. by incorporating the teaching of Pantoliano of fluorescent labeling and measuring using fluorescent polarization because one of ordinary skill in the art would have been motivated because of the teachings of Pantoliano that the advantages that quantitative information is provided for ligand binding to receptor (column 8, lines 18-67).

Claim 61 encompass a peptide comprising a label which is fluorescent and is coupled to the N-terminus. It would have been obvious to one of ordinary skill in the art at the time of the invention modify the peptide of Heery et al. by incorporating the teaching of Mathis and Pantoliano of fluorescent labeling to place the label at the N-terminus because one of ordinary skill in the art would have been motivated to any one of the labels

which would optimize the ligand binding to the receptor including FRET and polarization assay for the important screening for the therapeutic compounds.

14. Claims 32-45, 47-49 and 51-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heery et al.(Nature, 1997) in view of Harlow et al.(Antibodies, 1988), Montminy (Nature, 1997), Torchia et al. (Nature, 1997).

Heery et al. teaching and disclosure has been discussed above. Heery et al. do not teach the Elisa type immunoassay or the sandwich immunoassay variations encompassed claims 33-45.

Harlow et al. teach that immunoassays are well know to one of ordinary skill in the art and teach all the various immunoassays (page 555-616). Harlow et al. is a general antibody and immunology methodology which teaches antibody production against antigen and teaching many different immunoassays which can be adapted for particular needs to detect antigen.

The claims 32-45 limitation of immobilization of first receptor with sensor or vice versa is taught by Elisa assay of page 555 of Harlow et al. or the sandwich two antibody assay of page 556 of Harlow et al. Page 557-558 teach the process to decide immunoassay appropriate for antigen detection which includes many innunoasssay including the Elisa and sandwich assay. Harlow et al. teach the biotin labeling and detection

with avidin (page 591-592 and 340). Harlow et al. teach variations for each type of assay suitable for the desirable assay for antigen-antibody measurement. One of ordianry skill in the art would have been motivated to incorporate the teachings of Harlow et al. because the of the improvement in detection of peptides using Harlow's teaching and the general design of the Harlow methodology to adapt the assay for each different antigen. Further motivation is provided by Montminy and Torchia et al. who teach the importance of identifying ligands for therapeutic utility. Even more motivation is provided by Montminy (page 655, last line) teach that the identification of leucine rich motifs by Heery and Torchia allow for the eventual development of antagonists that can disrupt these complexes whose detection can be improved using the teachings of Harlow. The expectation of success is high because both Heery et al.(page 736) and Torchia et al.(page 863-864) make and use peptides based on the LXXLL motif from coactivators to show binding to receptors and Harlow et al. teach that that immunoassays are routine to one of ordinary skill in the art.

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Creighton teaches on page 25 amino acid and peptide detection.

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Pak, whose telephone number is (703) 305-7038. The examiner can normally be reached on Monday through Friday from 8:30 AM to 2:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Michael D. Pak

Michael Pak
Primary Patent Examiner
Art Unit 1646
7 September 2001

Yvonne Eyler

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